REVIEW ARTICLE

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Understanding Vaccine Safety and the Roles of the FDA and the CDC

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Throughout human history, epidemics and pandemics have resulted in untold suffering, localized reductions in population size, and damaged economies. Often, economic harm has caused greater loss of well-being than the infection itself. Increasing population density and economic and social changes, such as population shifts and the requirement for increased food production, have resulted in human encroachment into less populated areas of the globe. These factors bring people into closer contact with wildlife and arthropod vectors, as well as livestock and poultry, which increases the risk that zoonotic pathogens will spill over to humans. In the past two decades, bats have been reservoirs of three betacoronaviruses that have crossed the species barrier, causing severe acute respiratory syndrome (SARS)–like disease in humans. Recent outbreaks caused by noncoronaviruses such as pandemic influenza A (H1N1), Ebola, and Zika viruses underscore the threat of future outbreaks (Table 1). In the decades ahead, diseases caused by currently unknown viruses are likely to emerge as changes in human behavior continue to increase exposure to infectious organisms in the environment.

The development and widespread acceptance of vaccines will be crucial for controlling disease caused by pathogenic organisms, especially those that acquire the capability of efficient human-to-human transmission. As existing microbes evolve and new microbes emerge, nonpharmacologic interventions, including containment, isolation, and quarantine, will play a role in outbreak control, but vaccines will form the foundation for converting a viral pandemic into manageable endemic disease (Table 2). Containment of past viral pandemics has been accomplished without vaccines, but minimizing the morbidity and mortality associated with future pandemics is likely to be difficult to achieve without high rates of vaccine acceptance, especially for viruses that use the respiratory tract as a portal of entry.[1] A widespread understanding and acceptance of vaccines will be an integral aspect of public health strategies for limiting the consequences of future pandemics. This review discusses how vaccine safety and efficacy are evaluated, the pathways by which vaccines become authorized or licensed, and considerations addressed by advisory bodies in establishing vaccine recommendations.

DEFINING VACCINE SAFETY

The definition of a safe vaccine may differ from one person to another. Despite the overwhelming evidence of safety, vaccines have been associated with a small degree of untoward reactions, even when the vaccine is properly manufactured, handled, and administered (Table 3). A randomized clinical trial offers the most direct evidence of safety and is intended to control for factors that may influence study outcomes but cannot be directly determined. Randomized clinical trials are not optimal for detecting rare adverse events or adverse events with a delayed

Table 1. Viral Zoonotic Outbreaks since 1993.*

Year Identified	Pathogen or Disease	Location Where Disease First Described	Mortality Percentage	Viral Category	Source
1993	Sin Nombre virus†	New Mexico	About 35	Bunyavirus	Rodents, especially deer mice (*Peromyscus maniculatus*)
1999	Nipah virus	Malaysia	About 70	Paramyxovirus	Reservoir: fruit bats Vector: pigs, contaminated fruit
1999	West Nile virus	Uganda	<1	Flavivirus	Reservoir: birds Vector: culex mosquitoes
2002	SARS-CoV-1	China	9	Coronavirus	Reservoir: horseshoe bats Vector: palm civets
2009	Pandemic influenza A (H1N1) virus	Mexico	2	Orthomyxovirus	Swine
2012	Middle East respiratory syndrome virus	Saudi Arabia and Jordan	30	Coronavirus	Reservoir: bats Vector: dromedaries
2012	Acute flaccid myelitis	St. Louis	<1	Nonpolio enteroviruses	Reservoir: humans Fecal–oral spread
2013	Ebola virus	Uganda and Tanzania	50	Filovirus	Reservoir: monkeys Vector: nonhuman primates
2015	Zika virus	Uganda	8	Flavivirus	Reservoir: monkeys Vector: aedes mosquitoes
2019	SARS-CoV-2	China	<2	Coronavirus	Bats

* SARS-CoV-1 and SARS-CoV-2 denote severe acute respiratory syndrome coronavirus 1 and 2.
† Sin Nombre virus is the causative agent of hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome.

onset. A vaccine that has been shown to be safe in a randomized trial may be associated with a serious adverse event that does not occur until millions of doses have been administered. Vaccine safety in certain populations, such as children or immunocompromised patients, may not be determined in early trials, and issues regarding such subpopulations are generally evaluated in postlicensure assessments.

Typically, fewer than 10,000 persons have been enrolled in clinical trials of an experimental vaccine. For recently licensed vaccines, such as the rotavirus, human papillomavirus, varicella–zoster virus, and dengue virus vaccines, increasing numbers of persons have been included in prelicensure trials. For the experimental coronavirus disease 2019 (Covid-19) messenger RNA and replication-defective, adenoviral-vector vaccines, data were generated from 30,000 to 40,000 study participants. The size of a clinical trial is designed to maximize statistical power (the power to reject the null hypothesis that there is no significant difference between groups), minimize selection and allocation biases, and maximize the detection of adverse reactions. Depending on the incidence of the disease being studied, as the trial size increases, statistical power increases, but the trial may become more difficult to complete, with increasing development costs and prolongation of the time before a vaccine becomes available.

Table 2. Categories of Infectious Diseases.

Category	Definition
Pandemic	An epidemic that spreads between countries (e.g., Covid-19 was an epidemic when limited to China; with global spread, it became a pandemic)*
Epidemic	Sudden increase in cases above the expected incidence in a region where the disease is not permanently prevalent and is spreading from person to person
Endemic	Infection that is maintained at a baseline level in a geographic area; the infectious agent is always present in the population
Outbreak	Greater-than-anticipated increase in the number of cases of an endemic illness; if not quickly controlled, an outbreak can become an epidemic
Cluster	Increase above the number of expected cases in a place or time period
Sporadic disease	Disease that occurs infrequently and irregularly

* Covid-19 denotes coronavirus disease 2019.

Table 3. Historical Vaccine Safety Issues.

Year	Vaccine-Related Event	Event Consequence	Lessons Learned
1955	"Cutter Incident" involving killed polio vaccine	Some vaccine lots contained live poliovirus, resulting in cases of poliomyelitis	Increased regulation and oversight of vaccine manufacturing
1955–1963	10–30% of vaccines derived from monkey kidney cells contained simian virus 40	Prolonged follow-up showed no association with cancer in humans	No vaccines today contain simian virus 40
1976	Swine influenza vaccine associated with Guillain–Barré syndrome	Increased risk of approximately 1 case per 100,000 vaccinees	Influenza vaccines are monitored each year
1998	Hepatitis B vaccine possibly associated with multiple sclerosis	Thorough review by Institute of Medicine showed no association	
1998	Rotavirus vaccine associated with intussusception		Vaccine was removed from market
2005	Meningococcal vaccine possibly associated with Guillain–Barré syndrome	Thorough review of cases showed no association	
2007	*Haemophilus influenzae* type b vaccine contaminated with *Bacillus cereus*	No cases of bacterial infection found in vaccine recipients	Vaccine was recalled
2009	Pandemic influenza A (H1N1) vaccine associated with narcolepsy	Evaluation found an association in only one country (Finland) with one adjuvanted influenza vaccine	Vaccine was modified
2010	Rotavirus vaccine associated with porcine circovirus	Safety monitoring showed no safety issue in humans	
2013	Human papillomavirus vaccine vials contaminated with glass particles	Manufacturing error in one lot; no health problems reported	Lot was recalled
2017	Dengue vaccine associated with risk of severe dengue virus infection, depending on serostatus of recipient	Dengue-seronegative recipients of dengue vaccine are at risk for severe dengue if breakthrough infection occurs	Guidelines recommend serologic testing before vaccination and vaccine administration only in seropositive persons

As diseases prevented by vaccines become uncommon in the United States, the issue of adverse events after vaccination is receiving greater attention than the disease prevented by the vaccine. Fear of side effects has discouraged some people from being vaccinated, but for each licensed vaccine, the risk of an adverse reaction after vaccination is much lower than the risk of complications associated with the illness prevented.[2,3] After licensure or authorization, several robust Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) surveillance programs continue to monitor vaccine safety, including the Vaccine Adverse Event Reporting System, the Vaccine Safety Datalink, and the Clinical Immunization Safety Assessment Project.[4,5] A smartphone-based, active surveillance program, v-safe, was introduced to monitor the safety of Covid-19 vaccines.[6]

If indicated, data from postlicensure or postauthorization studies may be used to modify recommendations for vaccine use. One example of a modified recommendation based on postlicensure surveillance was the switch from use of oral poliovirus vaccine (OPV) to inactivated poliovirus vaccine (IPV), beginning in 1985. This change was based on the observation that despite remarkable efficacy, rare instances of vaccine-associated paralytic poliomyelitis developed among people with immunologic abnormalities or after reversion of a vaccine strain to neurovirulence, at a rate of approximately 1 case per 2.5 million OPV doses.[7] A switch to IPV was predicted accurately to offer a degree of protection that was similar to that of OPV but with a diminished risk of adverse reactions. Before the first polio vaccine became available in the United States, in 1955, a total of 15,000 cases of paralytic disease occurred annually, and many survivors were disabled for life. Since 1979, no cases of poliomyelitis have originated in this country. Routine vaccination with IPV continues to be recommended because of concern that the virus could be introduced by an infected traveler from a country where it still circulates.

Vaccines are neither completely safe nor always effective at disease prevention, leading some people to misunderstand the relative benefit and

risk of vaccination. A conclusion regarding safety may differ for persons who are more concerned about an adverse event developing in themselves or in their child and less concerned about societal benefits. An assessment regarding benefit and risk is not always straightforward, and the perspective of regulatory and advisory bodies may conflict with the perspective of a patient or a parent.[8] However, almost all severe adverse events reported after vaccination reflect a temporal association that is due to coincidence; almost none are causally associated with vaccine administration. The true cause of a serious adverse event after vaccination is almost always attributable to an unrelated factor that would have occurred in the absence of vaccine administration but may be difficult to identify.[9] With tens of thousands of vaccine doses administered each day in the United States, unrelated adverse events will occur after vaccination simply by chance. For example, in some children, the first symptoms of autism were noted to begin at about the age when the first measles vaccine was administered, at 12 to 15 months. This observation was interpreted incorrectly to support an association between autism and a measles-containing vaccine; this association has been soundly debunked.[10]

Adverse reactions that occur at a rate of less than 1 event per 10,000 persons are unlikely to be detected in prelicensure trials of 30,000 to 40,000 participants and may not be recognized until after widespread use of a vaccine. The incidence of the Guillain–Barré syndrome (GBS) after administration of a seasonal influenza vaccine is so low (an estimated 1 additional case of GBS per 1 million seasonal influenza vaccine doses administered) that available data do not permit a firm conclusion as to whether the vaccine causes GBS.[11] Because GBS occurs as a complication of influenza, the overall risk of GBS may be lower for persons who receive the influenza vaccine than for those who remain unvaccinated. Interpretation of a rare adverse event such as GBS requires both a standardized definition of the event (e.g., the definitions offered by the Brighton Collaboration) to ensure that the same event is being compared in vaccinated and unvaccinated persons and consideration of confounding issues, such as age, sex, season, time intervals, and status with respect to coexisting conditions.[12,13]

VACCINE LICENSING AND EMERGENCY USE AUTHORIZATION

The Center for Biologics Evaluation and Research (CBER) is the FDA branch responsible for regulatory oversight of vaccine development and licensure in the United States. The CBER regulates vaccines under authority derived from federal laws by applying specific regulations that address manufacturing consistency, clinical investigations, standards for safety and effectiveness, licensing, and product labeling.[14,15] For an experimental vaccine to be considered for licensure, the manufacturer must submit a Biologics License Application (BLA) demonstrating that the vaccine is safe and effective for its intended use. Review of the application includes adherence to ethical and scientific quality standards, inspection of clinical study sites, statistical analyses of primary data from clinical studies, data on assay validation, detailed manufacturing information, and inspection of manufacturing facilities. Factors that the FDA considers when deciding whether to license or authorize a vaccine include the prevalence and severity of the disease being prevented, the frequency and severity of an adverse reaction after immunization, and the effectiveness of the vaccine in preventing the disease in the target population.[4] The normal pathway to regulatory approval of a vaccine is a deliberative process; several years are needed in order to comply with mandatory requirements. In some instances, the CBER may seek advice from an external advisory committee, the Vaccines and Related Biological Products Advisory Committee, to assist in assessing benefits and risks.

In certain circumstances, such as a national emergency declared by the Secretary of Health and Human Services, the FDA may permit an experimental vaccine to be used outside the standard regulatory framework. The Public Readiness and Emergency Preparedness Act was enacted in 2005 to identify a public health emergency and to facilitate a coordinated response, including emergency use authorization (EUA) for specific countermeasures.[15] Depending on the urgency, the FDA may grant an EUA, which allows for rapid deployment of an unlicensed vaccine in order to provide individual and community protection as quickly as possible.[16,17] Covid-19 vaccines, for protection against severe acute respira-

tory syndrome coronavirus 2 (SARS-CoV-2), were the first non–previously licensed vaccines made available under an EUA. The expedited review process for an unlicensed vaccine makes it available much more rapidly than the traditional BLA review process. Despite the authorization of Covid-19 vaccines under an expedited review process, a meticulous evaluation of vaccine safety was undertaken, which was similar to the evaluation used before issuing a BLA. Federal money was made available to leverage the financial risk for Covid-19 vaccine manufacturers, enabling a shorter development time.[18,19] For example, manufacturing facilities for vaccine production were constructed before efficacy results from trials were available, a sequence that is unlikely to occur with standard vaccines. Despite the compressed time period, no assessment of safety was abridged.

A public health emergency related to Covid-19 was declared by the Secretary of Health and Human Services on January 31, 2020. Because no licensed vaccines were available, the FDA issued guidance for an EUA of experimental RNA, DNA, protein, and replication-defective viral vector–based vaccines.[17] The availability of an authorized vaccine (as opposed to a licensed vaccine) was to remain in effect only for the duration of the public health emergency or until the vaccine became licensed. FDA guidance noted the expectation that results from clinical trials would continue to be collected and submitted to support a BLA.

OTHER FDA PATHWAYS

To encourage and facilitate the development and availability of a needed vaccine, an expedited approval process is available when an extended period would be required to measure the clinical benefit. The FDA has defined four programs that warrant an expedited review: fast-track designation, breakthrough-therapy designation, accelerated approval, and priority-review designation. These pathways use a nonclinical surrogate end point to shorten the time until the vaccine is available. The clinical benefit of the surrogate end point must be documented in a subsequent clinical trial.[19]

Expanded access to an investigational new drug (sometimes referred to as compassionate use) is an alternative pathway to gain access to an experimental vaccine and does not require declaration of a public health emergency.[20] Expanded access is considered when an investigational vaccine is likely to be helpful in a life-threatening situation, no similar or satisfactory alternative vaccine is available, enrollment in an existing clinical trial is not possible, and time does not allow for preparation and submission of a BLA. A vaccine in this category has not been licensed and its safety and efficacy have not been established, but the potential benefit is thought to justify the possible risk associated with the vaccine. This pathway was used to make experimental meningococcal B vaccines available on several college campuses during clusters of disease, starting in 2013.[21]

The Animal Rule pathway was established to permit licensure of a vaccine as a countermeasure for lethal or permanently disabling conditions when traditional human efficacy studies are not ethical and field trials or randomized clinical trials to evaluate effectiveness are not feasible.[22] This pathway is a route of last resort when approval under any other mechanism is not possible. In 2015, the anthrax vaccine was the first vaccine to receive approval for a new indication through the Animal Rule pathway and was the first to be approved for prevention of inhalational anthrax.[23]

Once the FDA authorizes or licenses a vaccine, recommendations for its use are developed by the Advisory Committee on Immunization Practices (ACIP) on the basis of several considerations (Table 4). The ACIP is an external advisory committee that provides advice to the director of the CDC regarding use of vaccines in the civilian population.[24] Once a vaccine is licensed by the FDA, recommendations for its use are published in the *Morbidity and Mortality Weekly Report*. Individual states establish vaccination requirements for specific communicable diseases for children who attend public schools, and these requirements often apply to children in private schools and those in child-care facilities.

ECONOMIC CONSIDERATIONS

Economic factors are not evaluated by CBER in considering licensure or authorization of an experimental vaccine. In contrast, the ACIP charter states that deliberations should include an "economic analysis."[24,25] Although a specific cost–benefit threshold has not been established for inclusion of a vaccine in the immunization pro-

gram, an economic analysis provides an understanding of the effect of a new recommendation on the overall immunization schedule. A frequently used economic metric is quality-adjusted life-years (QALYs) gained. This analysis is based on the cost per unit of health, expressed as QALYs, and is calculated as the incremental cost-effectiveness ratio between options, such as vaccine versus no vaccine. QALYs remain controversial because the threshold for accepting a vaccine as cost-effective cannot be defined easily. Individual judgments form the basis for a decision regarding a recommendation rather than a calculated dollar threshold that reflects inflation and economic growth. In addition, QALYs tend to favor vaccines against common diseases associated with relatively low morbidity and mortality over vaccines against less common illnesses associated with greater morbidity and mortality.[26]

Table 4. Issues That the FDA and CDC Consider When Determining Vaccine Licensure and Recommendations.*

Safety
Efficacy
Equity
Public health effect
Cost effectiveness
Effect on community (herd) immunity
Vaccine supply and storage
Compatibility with existing vaccine schedule
Public acceptance of vaccine
Age when disease is most likely to occur
Effect of age on immune response
Duration of immune response
Need for boosters
Minimizing number of doses
Simplification of immunization schedule

* CDC denotes Centers for Disease Control and Prevention, and FDA Food and Drug Administration.

Table 5. People Who Benefit from Community Protection (Herd Immunity).

Children and infants too young to be immunized
Pregnant people
People in whom vaccine-induced immunity has waned
Immunosuppressed patients who cannot be immunized
Elderly persons who may not have an adequate immune response
People with inadequate access to immunizations
People who remain unvaccinated by choice

SCHOOL VACCINE REQUIREMENTS

Because most licensed vaccines are intended to prevent infections that are transmitted from person to person, vaccination not only offers protection to the vaccine recipient but also helps to ensure community protection (Table 5). Since enactment of the first vaccination requirement to prevent smallpox transmission in schools, in 1855, state-imposed school vaccination requirements have been instrumental in the prevention and control of vaccine-preventable diseases. In 1905, the U.S. Supreme Court issued a landmark ruling in *Jacobson v. Massachusetts* upholding the right of states to compel vaccination for students.[27] The Court determined that a health regulation requiring smallpox vaccination was a reasonable exercise of state authority.

Some persons and communities disagree with school vaccine requirements on the basis of religious or philosophical beliefs and express concern that state immunization requirements interfere with individual autonomy. However, no specific constitutional right to a vaccine exemption exists. All 50 states require vaccines for students, although exemptions vary from state to state. As of January 2022, all states grant vaccine exemptions for medical reasons, 44 states (and Washington, D.C.) grant religious exemptions, and 15 states allow philosophical exemptions when parents object to immunizations on the basis of personal or moral beliefs.[28] State laws also permit the exclusion of unvaccinated students from school attendance in the event of a vaccine-preventable outbreak. Studies have shown that when persons exercise vaccine exemptions, it places them and their communities at risk for contracting vaccine-preventable infections.[29,30] Because diseases that vaccines currently control occur at low rates, challenges to school vaccination requirements are likely to continue to arise. Those who support such challenges do not understand that even though rates of disease are low, the agents that cause communicable diseases continue to circulate, and any relaxation of school vaccine requirements increases the possibility that currently controlled diseases will no longer be controlled, putting all children at risk.

CONCLUSIONS

We live in an era when the lowest rates of vaccine-preventable diseases in the history of the United States strongly correlate with the highest rates of vaccination. Vaccines have resulted in the global elimination of disease caused by several viruses, including variola virus (smallpox), as well as wild-type polioviruses 2 and 3. Before the eradication of rinderpest virus, which causes cattle plague, in 2012 as a consequence of effective vaccination programs, this virus was associated with nearly 100% mortality among infected cattle, leading to periodic, localized human famines.[31]

Life expectancy at birth is one measure of a population's health. In 2020, the life expectancy at birth for the total U.S. population was 77.3 years, a decline of 1.5 years from 2019 (78.8 years) that was largely attributable to deaths from SARS-CoV-2 infections.[32] SARS-CoV-2 infection was the third leading cause of death in the United States in both 2020 and 2021. Infection with either SARS-CoV-1 or Middle East respiratory syndrome (MERS) coronavirus results in higher rates of death than does infection with SARS-CoV-2, which indicates that the consequences of the current coronavirus pandemic could have been much worse. The prospect of future pandemics is troubling, but rapid scientific advances have shown that with improved preparation, future outbreaks can be controlled. Controlling future outbreaks will depend on continued funding for basic research and on maintenance of a robust vaccine industry, with improvements in manufacturing capacity, distribution, and storage, as well as an improved public health infrastructure for vaccine administration around the globe.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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